Heterocycle Synthesis

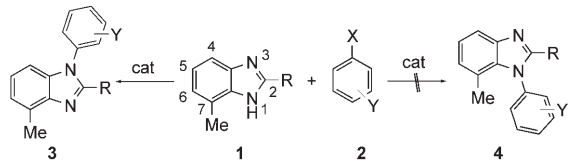
DOI: 10.1002/ange.200702542

A Palladium-Catalyzed Regiospecific Synthesis of *N*-Aryl Benzimidazoles**

*Nan Zheng, Kevin W. Anderson, Xiaohua Huang, Hanh Nho Nguyen, and Stephen L. Buchwald**

Benzimidazoles are a class of privileged core structures that are found in a broad spectrum of biologically active compounds such as nonpeptide luteinizing hormone-releasing hormone (LHRH) antagonist,[1] lymphocyte specific kinase (Lck) inhibitor,[2] *N*-methyl-D-aspartate (NMDA) antagonist,[3] neuropeptide Y Y1 receptor antagonist,[4] nonpeptide thrombin inhibitor,[5] 5-lipoxygenase inhibitor,[6] factor Xa (FXa) inhibitor,[7] and poly(ADP-ribose)polymerase (PRAP) inhibitor.[8] Benzimidazoles have also been widely used in fungicides, herbicides, and other veterinary application.[9] In addition, they have been frequently used as the backbone in dyes[10] and high-temperature polymers.[11] Not surprisingly, numerous efforts have been devoted to the development of methods for the preparation of benzimidazoles.[12]

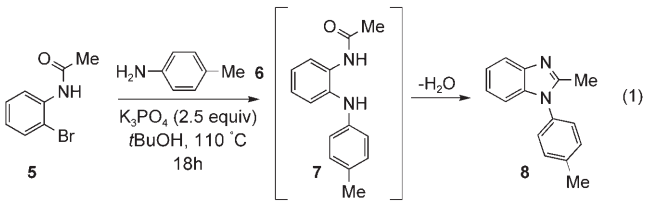
Despite these efforts, the preparation of N-substituted benzimidazoles in regioisomerically pure form remains a challenging issue. One of the most common methods for the synthesis of benzimidazoles involves the condensation of a suitably substituted 1,2-diaminoarene with a carboxylic acid or an equivalent.[12] *ortho*-Nitroaniline can also be used in the place of the 1,2-diaminoarene under reducing conditions.[13] However, the preparation of N-1-substituted benzimidazoles using these methods depends on the availability of the requisite 1,2-diaminoarene or *ortho*-nitroaniline, which are oftentimes difficult to prepare.[14] Benzimidazoles unsubstituted at N-1 such as **1** are more accessible. However, the *N*-arylation of these compounds is often not straightforward. Several issues contribute to this problem. In particular, the *N*-arylation of benzimidazoles with electron-rich aryl halides often requires both forcing conditions and/or the use of aryl iodides.[15] Additionally, these reactions are very sensitive to steric hindrance. The presence of the C-2 substituent ($R \neq H$) on the benzimidazoles or the use of *o*-substituted aryl halides further reduces the efficiency of these methods. To our knowledge, no examples of the arylation of C-2-substituted benzimidazoles with *o*-substituted aryl halides have been reported. A further problem is depicted in Scheme 1. The



Scheme 1. *N*-Arylation of benzimdazoles at N-1.

introduction of a substituent on the benzimidazole ring (such as the C-7 methyl group of **1**) renders the N-1 and N-3 atoms inequivalent. The steric environment of the N-1 and N-3 atoms generally dictates the regioselectivity for the *N*-arylation; the less hindered nitrogen atom is preferentially arylated. For example, while the *N*-arylation of **1** should provide **3**, no arylation protocol exists for the conversion of **1** to **4**.

During the course of our work on developing improved methods for palladium-catalyzed carbon–nitrogen bond-forming processes, we examined the amination of *ortho*-bromoacetanilide **5** [Eq. (1)]. In contrast to what we had observed with the reactions of the *para* and *meta* isomers of **5**,[16] the amination product **7** was not observed. Instead, benzimidazole **8** was isolated in excellent yield, presumably formed by the in situ dehydration of **7**. This unexpected finding led us to ask whether we could extend this reaction into a general and convergent method to prepare *N*-arylated benzimidazoles in regioisomerically pure form. By choosing a suitably substituted *o*-haloanilide, we envisioned that the Pd-catalyzed amination protocol shown in Equation (1) could be used to prepare either regioisomer (for example, **3** and **4**). Herein, we report our efforts towards this goal, resulting in a catalytic method that allows the preparation of a variety of *N*-aryl benzimidazoles in regioisomerically pure form.[17]



(1)

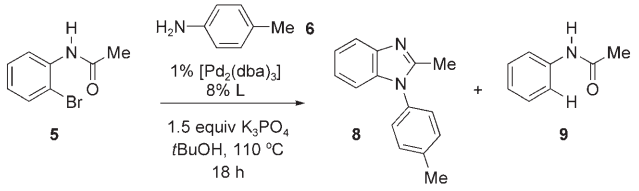
[*] Dr. N. Zheng, Dr. K. W. Anderson, Dr. X. Huang, Dr. H. N. Nguyen, Prof. Dr. S. L. Buchwald
Department of Chemistry, Room 18-490
Massachusetts Institute of Technology
Cambridge, MA 02139 (USA)
Fax: (+1) 617-253-3297
E-mail: sbuchwal@mit.edu

[**] We thank the National Institutes of Health (GM 58160) and the National Cancer Institute (Cancer Training Grant CA09112) for support of this work. N.Z. acknowledges the National Institutes of Health for a postdoctoral fellowship (F32-GM074407). We are grateful to Merck, Amgen, and Boehringer Ingelheim for unrestricted support. The Varian 300 and 500 MHz instruments used in this study were purchased with funding from the National Science Foundation (CHE 9808061 and DBI 9729592). We thank Dr. Takashi Ikawa for developing a protocol for the conversion of **24** into **25**.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

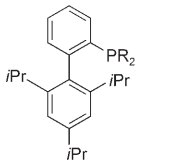
The coupling of 2-bromoacetanilide **5** and *p*-toluidine **6** was studied as a model system for optimizing the formation of *N*-aryl benzimidazoles. Screening experiments revealed *t*BuOH and K_3PO_4 to be the optimal combination of solvent and base. Using these conditions, we examined the efficiency of a series of ligands (Table 1). One common side reaction was the reduction of 2-bromoacetanilide **5** to acetanilide **9**. Variable amounts of **9** were observed during these ligand-screening experiments. The catalysts derived from two ligands, XPhos[18] (**L1**) and RuPhos[19] (**L5**), showed superior activity in the coupling reaction. With either ligand, a high yield of **8** was realized.

Table 1: Screening of phosphine ligands for palladium-catalyzed amination of *ortho*-haloanilides.

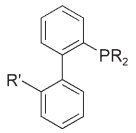


L	% conv. (**5**)[a,b]	Yield of **8** [%][a,b]
L1 (XPhos)	89	86
L2 (*t*BuXPhos)	38	13
L3 (JohnPhos)	41	14
L4 (DavePhos)	46	6
L5 (RuPhos)	100	100
L6 (*rac*-Binap)	26	0
L7	42	21
L8	32	0
L9	29	0

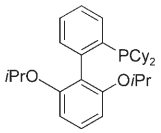
[a] GC results using dodecane as an internal standard. [b] Average of two runs.



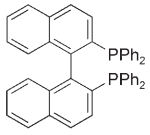
L1: R = Cy, XPhos
L2: R = *t*Bu, *t*BuXPhos



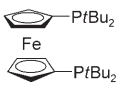
L3: R = *t*Bu, R' = H, JohnPhos
L4: R = Cy, R' = NMe_2, DavePhos



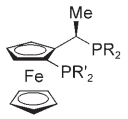
L5: RuPhos



L6: Binap



L7



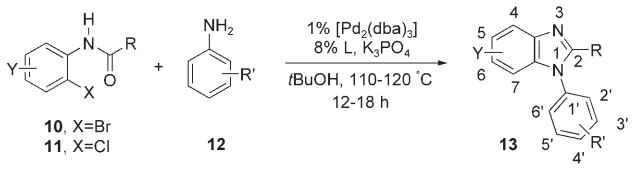
L8: R = Cy, R' = Cy
L9: R = *t*Bu, R' = Ph

With a useful catalyst system (1 mol% $[Pd_2(dba)_3]$ (dba = *trans*,*trans*-dibenzylideneacetone), 8 mol% XPhos or RuPhos (Pd:L = 1:4), and 2.5 equiv K_3PO_4 in *t*BuOH) in hand, we set out to examine the substrate scope of the method for the preparation of *N*-aryl benzimidazoles (Table 2). The method tolerated a wide range of amide substituents (R group) including methyl, isobutyl, *tert*-butyl, phenyl, furyl, cyclopropyl, and CH_2OBn. A variety of substituents (R′) could also be accommodated at the *ortho*, *meta*, or *para* positions of the aniline moiety. Examples of the R′ group included methyl, methoxy, chloride, and isopropyl groups. Of note is that this method is effective for the preparation of *N*-aryl benzimidazoles in which the C-2′ position can be substituted with substituents as large as *i*Pr. Moreover, the method is amenable to the preparation of compounds containing substituents at both the C-2 position of the benzimidazole and the C-2′ position of the N-1 aryl group. While the former can sometimes be accessed with difficulty, to our knowledge, the latter have never been prepared by direct *N*-arylation processes. However, with sterically more hindered anilines such as *ortho*, *ortho*′-disubstituted anilines, the amination process was too slow to be preparatively useful. In some instances, either the position or electronic nature of the Y group (the substituent of aryl halide **10** or **11**) affected the carbon–nitrogen coupling. For example, when Y was a strong electron-withdrawing group (e.g., cyanide) and *para* to the amide, hydrolysis of the amide group necessitated the use of an increased quantity of the catalyst. In addition, if the substituent, Y, was strongly electron-donating (e.g., methoxy) and *para* to the bromide, the rate of the amination reaction was too slow to be synthetically useful. Otherwise, the efficiency of the reaction was independent of the electronic character and/or the position of the Y group. We were also able to extend this method to heteroaromatic halides as coupling partners. In this way, 5-azabenzimidazole **13r** and 7-azabenzimidazole **13s** were efficiently prepared. Aryl bromides and aryl chlorides were both suitable substrates for the process. In most cases, XPhos and RuPhos could be used interchangeably. However, when hindered aryl halides (e.g., **14a**) were used in the coupling, RuPhos gave far superior results.

Having established the substrate scope for this method, we turned our attention to the preparation of pairs of *N*-aryl benzimidazole regioisomers, each in isomerically pure form. Indeed, three pairs of isomeric aryl bromides were successfully coupled with three different aromatic amines to provide benzimidazoles in regioisomerically pure form (Table 3). Using the optimized conditions (RuPhos), aryl bromides **14a** and **14b** were converted in a straightforward manner to benzimidazoles **15a** and **15b**. However, some further optimization was needed for the synthesis of the other two pairs of benzimidazoles due to the electronic effects of the Y groups (see above). While the coupling reaction of aryl bromide **16a** and *p*-anisidine **21** proceeded as expected under the standard conditions, the corresponding reaction of aryl bromide **16b** was significantly slower. Increasing the quantity of catalyst (2 mol% $[Pd_2(dba)_3]$ and 16 mol% RuPhos) allowed the reaction to go to completion in 18 h and provided benzimidazole **17b** in 90% yield. Similarly, increasing the catalyst loading was required in the coupling of aryl bromide **18a** and aniline **22** to overcome the competitive hydrolysis of **18a** to **23**. The coupling of aryl bromide **18b** and aniline **22** was conducted at a lower temperature (100 °C) to maximize the yield of benzimidazole **19b**.

The preparation of *N*-aryl benzimidazoles using this method required the aryl halides bearing an amide group *ortho* to a halide. In principle, the requisite starting material

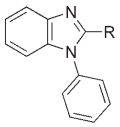
Table 2: Palladium-catalyzed synthesis of *N*-aryl benzimidazoles.



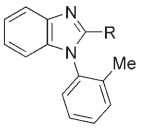
10, X=Br
11, X=Cl

12

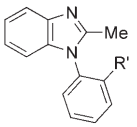
13



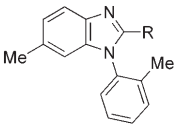
13a (R = *i*Bu, X = Br, **L1**, 89%)
13b (R = *t*Bu, X = Br, **L1**, 89%)[a]



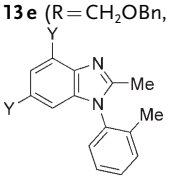
13c (R = Me, X = Br, **L1**, 56%)
13d (R = *i*Bu, X = Br, **L1**, 67%)
13e (R = CH_2OBn, X = Br, **L5**, 82%)



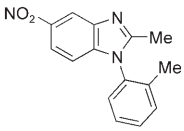
13f (R′ = *i*Pr, X = Br, **L1**, 85%)
13g (R′ = OMe, X = Br, **L1**, 83%)
13h (R′ = Cl, X = Br, **L1**, 59%)



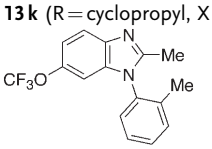
13i (R = Ph, X = Br, **L5**, 86%)
13j (R = furyl, X = Br, **L5**, 86%)
13k (R = cyclopropyl, X = Br, **L5**, 83%)



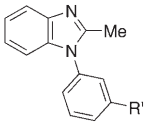
13l (Y = Me, X = Br, **L1**, 91%)
13m (Y = F, X = Br, **L1**, 68%)



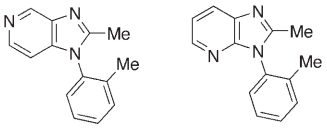
13n (X = Cl, **L5**, 87%)



13o (X = Br, **L5**, 74%)



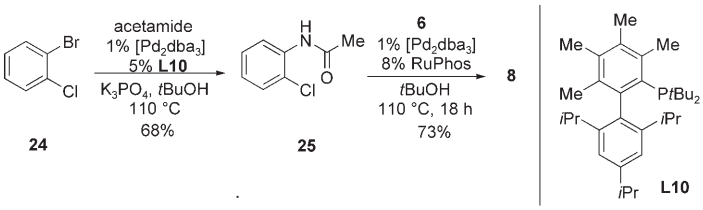
13p (R′ = Cl, X = Br, **L5**, 80%)
13q (R′ = NH_2, X = Br, **L1**, 52%)



13r (X = Cl, **L5**, 88%) **13s** (X = Cl, **L5**, 83%)

[a] 4 N HCl iin 1,4-dioxane, 100 °C.

could be prepared by performing amidation on an aromatic compound bearing two *ortho*-disposed halides. This approach is illustrated with one example shown in Scheme 2. 1-Bromo-2-chlorobenzene **24** was first preferentially coupled with acetamide using a catalyst system composed of $[Pd_2(dba)_3]$, tetramethyl *t*BuXPhos (**L10**), and K_3PO_4 in *t*BuOH.[20] Subsequently, amide **25** and *p*-toluidine **6** were combined by using the method described earlier to produce benzimidazole **8**.



Scheme 2. Synthesis of *N*-aryl benzimidazoles by sequential amidation/amination.

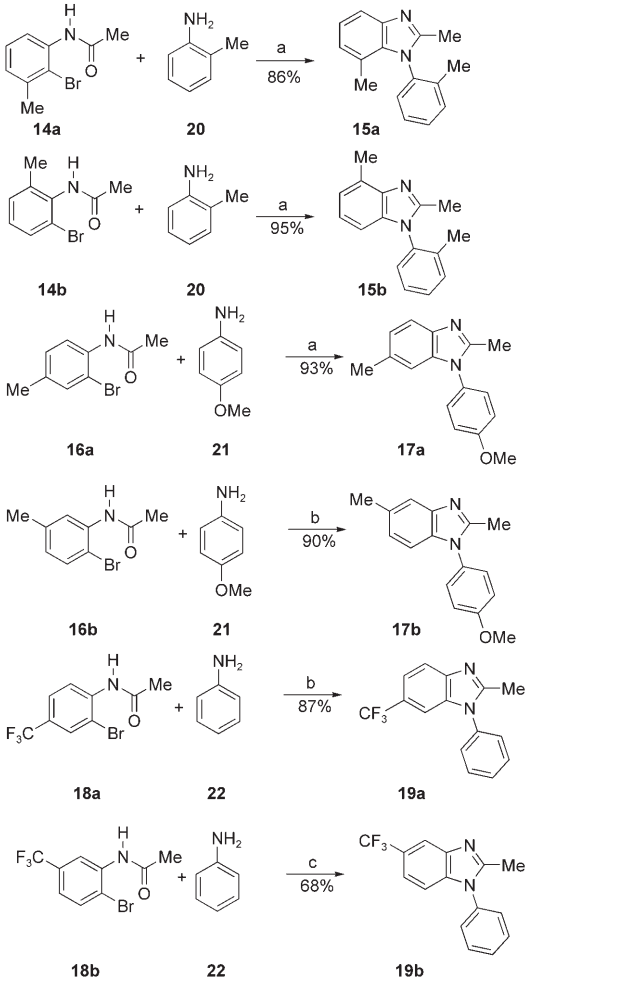
In summary, we have developed a catalytic method for the synthesis of *N*-aryl benzimidazoles. This method provides a protocol that enables the synthesis of *N*-aryl benzimidazoles in regioisomerically pure form, while displaying good functional group tolerance. We expect it will become a valuable addition to the methods available for the synthesis of benzimidazoles, an important class of heterocycles.

Experimental Section

General procedure for Pd-catalyzed synthesis of *N*-aryl benzimidazoles (Table 2 and Table 3): An oven-dried Schlenk tube containing a Teflon-coated stir bar was charged with $[Pd_2(dba)_3]$ (4.6 mg, 0.005 mmol, 2.0 mol% Pd), ligand **L1** or **L5** (0.04 mmol, 8 mol%), *ortho*-haloanilides (0.5 mmol), aromatic amines (0.75 mmol) and K_3PO_4 (265.3 mg, 1.25 mmol). The Schlenk tube was capped with a Teflon screw cap and then evacuated and backfilled with argon (3 cycles). *t*BuOH (1.0 mL) was added to the Schlenk tube under a positive flow of argon (liquid aromatic amines were added to the Schlenk tube at this point). The Schlenk tube was sealed and put into a pre-heated oil bath at 110 °C. After stirring for 18 h, the reaction mixture was allowed to cool to room temperature and diluted with dichloromethane (ca. 4 mL). The diluted mixture was filtered through Celite with the aid of dichloromethane. The filtrate was concentrated under vacuum to give a residual that was purified by flash chromatography on silica gel.

Received: June 12, 2007
Published online: August 23, 2007

Table 3: Palladium-catalyzed synthesis of regioisomeric *N*-aryl benzimidazoles.



[a] 1 mol% $[Pd_2(dba)_3]$, 8 mol% RuPhos, K_3PO_4, *t*BuOH, 110 °C. [b] 2 mol% $[Pd_2(dba)_3]$, 16 mol% RuPhos, K_3PO_4, *t*BuOH, 110 °C. [c] 1 mol% $[Pd_2(dba)_3]$, 8 mol% RuPhos, K_3PO_4, *t*BuOH, 100 °C.

Keywords: amination · heterocycles · *N*-aryl benzimidazole · palladium

[1] Y. Li, M. Kataoka, M. Tatsuta, K. Yasoshima, T. Yura, K. Urbahns, A. Kiba, N. Yamamoto, J. B. Gupta, K. Hashimoto, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 805 – 807.

[2] M. Sabat, J. C. Vanrens, M. J. Laufersweiler, T. A. Brugel, J. Maier, A. Golebiowski, B. De, V. Easwaran, L. C. Hsieh, R. L. Walter, M. J. Mekel, A. Evdokimov, M. J. Janusz, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5973 – 5977.

[3] R. B. Baudy, H. Fletcher III, J. P. Yardley, M. M. Zaleska, D. R. Bramlett, R. P. Tasse, D. M. Kowal, A. H. Katz, J. A. Moyer, M. Abou-Gharbia, *J. Med. Chem.* **2001**, *44*, 1516 – 1529.

[4] H. Zarrinmayeh, A. M. Nunes, P. L. Ornstein, D. M. Zimmerman, M. B. Arnold, D. A. Schober, S. L. Gackenheimer , R. F. Bruns, P. A. Hipskind, T. C. Britton, B. E. Cantrell, D. R. Gehlert, *J. Med. Chem.* **1998**, *41*, 2709 – 2719.

[5] N. H. Hauel, H. Nar, H. Priepke, U. Ries, J. Stassen, W. Wienen, *J. Med. Chem.* **2002**, *45*, 1757 – 1766.

[6] H. Nakano, T. Inoue, N. Kawasaki, H. Miyataka, H. Matsumoto, T. Taguchi, N. Inagaki, H. Nagai, T. Satoh, *Bioorg. Med. Chem.* **2000**, *8*, 373 – 380.

[7] H. Ueno, S. Katoh, K. Yokota, J. Hoshi, M. Hayashi, I. Uchida, K. Aisaka, Y. Hase, H. Cho, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4281 – 4286.

[8] A. W. White, R. Almassy, A. H. Calvert, N. J. Curtin, R. J. Griffin, Z. Hostomsky, K. Maegley, D. R. Newell, S. Srinivasan, B. T. Golding, *J. Med. Chem.* **2000**, *43*, 4084 – 4097.

[9] J. Velík, V. Baliharova, J. Fink-Gremmels. S. Bull, J. Lamka, L. Skalova, *Res. Vet. Sci.* **2004**, *76*, 95 – 108, and reference therein.

[10] G. Schwartz, K. Fehse, M. Pfeiffer, K. Walzer, K. Leo, *Appl. Phys. Lett.* **2006**, *89*, 083509.

[11] J. A. Asensio, P. Gomez-Romero, *Fuel Cells* **2005**, *5*, 336 – 343.

[12] M. R. Grimmett in *Imidazole and Benzimidazole Synthesis, Best Synthetic methods* (Ed.: O. Meth-Cohn), Academic, London, **1997**.

[13] D. Yang, D. Fokas, J. Li, L. Yu, C. M. Baldino, *Synthesis* **2005**, 47 – 56, and references therein.

[14] W. J. Ebenezer, M. G. Hutchings, K. Jones, D. A. Lambert, I. Watt, *Tetrahedron Lett.* **2007**, *48*, 1641 – 1643.

[15] a) L. Liu, M. Frohn, N. Xi, C. Dominguez, R. Hungate, P. J. Reider, *J. Org. Chem.* **2005**, *70*, 10135 – 10138; b) X. Lv, W. Bao, *J. Org. Chem.* **2007**, *72*, 3863 – 3867; c) K. W. Anderson, R. E. Tundel, T. Ikawa, R. A. Altman, S. L. Buchwald, *Angew. Chem.* **2006**, *118*, 6673 – 6677; *Angew. Chem. Int. Ed.* **2006**, *45*, 6523 – 6527.

[16] M. C. Harris, X. Huang, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 2885 – 2888.

[17] During the preparation of this manuscript, a conceptually related Cu-catalyzed process for the preparation of *N*-alkyl benzimidazoles appeared: B. Zou, Q. Yuan, D. Ma, *Angew. Chem.* **2007**, *119*, 2652 – 2655; *Angew. Chem. Int. Ed.* **2007**, *46*, 2598 – 2601.

[18] X. Huang, K. W. Anderson, D. Zim, L. Jiang, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 6653 – 6655.

[19] M. D. Charles, P. Schultz, S. L. Buchwald, *Org. Lett.* **2005**, *7*, 3965 – 3968.

[20] T. Ikawa, T. E. Barder, M. Biscoe, S. L. Buchwald, unpublished results.

